First Trimester Screening for Early Onset Preeclampsia
“The Predicament of the Prediction and Prognostication of Preeclampsia”
James N Martin Jr

The Speaker Has No Conflicts of Interest

Preeclampsia Essentials, Epidemiology & Challenges to First Trimester Screening:
Fundamentals & The State of Knowledge

RISING INCIDENCE of Preeclampsia in USA

### Preeclampsia: By the Numbers

- 500,000 cases/year in U.S.A.
- 100,000 maternal deaths/year
- 500,000 fetal & newborn deaths/year

**For perspective...**
- 8x higher incidence than heart attack
- 25x higher incidence than prostate cancer
- 50x higher incidence than colon cancer

*Originally described by Hippocrates... 2,400 years ago*

**And still today, there are...**
- No Diagnostic Test(s)
- No Treatment(s)

---

### Preeclampsia: More than Late Pregnancy HTN, Proteinuria, and Edema

- 5-10% of all pregnancies (500,000/year)
- 15% of perinatal morbidity/mortality (100,000 maternal deaths/year)
- **Short term:** Maternal headache, blurry vision, seizure, multiorgan failure, fetal growth restriction, maternal-fetal death
- **Long term:** Increased maternal CV events, future adult stroke, metabolic disease, and epilepsy for the children

26 wks
8.6 ounces
Delivered due to Severe Preeclampsia
(from Dr. Mark Santillan-Iowa)

---

### Placental bed vascular remodeling is abnormal in PE

- Put a "funnel at the end of a hose" reduces velocity of flow (1-2 m/sec to 10cm/sec)
- Minimal (50%) affect on volume of flow

*P Parham 2004*
As a consequence of abnormal placentation and the generation of multiple abnormal factors, there are widespread downstream effects to the fetus and mother.

**Fetal Manifestations of PE**

- Vascular Stillbirth
- Abnormal Uterine & Fetal Dopplers
- Fetal Growth Restriction
- Placental Abruption
- Oligohydramnios

**Maternal Manifestations of PE**

- Blood Pressure
- Capillary Leak
- Fibrinolysis Hemolysis
- Symptoms
- Normal
- Mild
- Severe
- Epigastric pain
- CNS
- Bleeding
- Nausea/vomiting
- Proteinuria
- Facial edema
- Pulmonary edema
- Ascites
- Pleural effusions
- HELLP
- Renal failure
- Low platelet
- Liver enzymes
- DIC

Adapted from an Illustration by Dr. John Barton, Lexington, KY.
MATERNAL MORBIDITY with PE occurs 10-50x >>Mortality

- Major life-threatening morbidity “near miss” or SAMM (severe acute maternal morbidity)
- **Dominant Causes: Hemorrhage & Hypertension**
- Maternal Morbidity Audit: Netherlands
  - 358,874 deliveries 2004-2006
  - 2552 SAMMs
  - Substandard care in 53 of 67 women investigated or 79.1%

Van Dillen J, Mesman JAJM et al, BJOG 2010;117:416-421

---

PE: The Disease of Theories

- Poor Placentation → Placental Dysfunction → Vascular Dysfunction → Renal Changes
- Poor Placentation
- Placental Dysfunction
- Vascular Dysfunction
- Renal Changes

- Altered Immunology
- Hyperinflammation
- Antiangiogenesis
- Calcium deficiency
- Increased Oxidative Stress
- Endothelial Dysfunction
- RAS Changes

PREECLAMPSIA

---

LDA Initiated <16 Weeks Gestation

- Roberge* 2013 Meta-Analysis of LDA
  - “Severe” PE relative risk = 0.18 (95% CI 0.08-0.41) vs 0.65 (95% CI 0.4-1.07) with LDA started <16 weeks
- Cochrane Review 2007 (46 trials, 32,891 women)
  - PE relative risk = 0.83 (95% CI 0.77-0.89)
  - NNT = 72 to prevent one case of PE
  - PE relative risk = 0.90 (95% CI 0.84-0.97)
  - NNT = 114 to prevent one case of PE

* Roberge S, Nicolaides KH et al. Ultrasound Obstet Gynecol 2013;41:491-499

Both Cochrane & PARIS found statistically significant reductions in preterm birth
Criteria to Justify Screening for a Disease
Wilson JMG, Jungner G. Principles & Practice of Screening for Disease [WHO 1968]

• **CONDITION:**
  - Important health problem
  - Recognizable latent or early symptomatic stage
  - Natural history of the disease is understood

• **TEST:** Suitable test or examination, acceptable to patients

• **Rx:** Accepted treatment for patients with recognized disease

• **SCREENING PROGRAM:**
  - Facilities for Dx/Rx available
  - Agreed policy on whom to treat as patients
  - Cost of case finding/Dx/Rx should be economically feasible and on a continuing process going forward

Screening Strategies: Maternal Factors

• **NICE/UK:**
  - High Risk: Prior Pregnancy Hypertension/Chronic Kidney Disease/Autoimmune Disease/Diabetes or I/II/CHTN
  - Moderate Risk: First Pregnancy/Age ≥40/LEP>10yrs/BMI≥35 @First Visit/Family History of PE/Multiple Gestation

• **WHO:** Prior PE/Diabetes/CHTN/Renal Disease/Autoimmune Disease/Multiple Gestation

• **SOGC:**
  - High Risk: Prior PE/APA+/Pre-existing Medical Condition/Age≥40 BMI≥35/Family History of PE/First Pregnancy/LEP>10yrs/Booking SBP>130 or DBP>80/Multiple Gestation
  - Moderate Risk: Ethnicity (Nordic/Black/SouthAsian/Pacific Island)/Lower SES/Non-Smoking/Heritable Thrombophilia/Increased Pre-Pregnancy Triglycerides/Family History of Early Onset CV Disease/Cocaine/Meth Use/LEP>130/ART/New Partner/CHTN/Excessive Weight Gain During Pregnancy/Infection During Pregnancy

• **ACOG:** Prior Early Onset PE or PTD <34 wks/PE ≥1 Prior Pregnancy
Maternal Risk Factors for PE Prediction

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AUC</th>
<th>95% CI</th>
<th>PP detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early PreE</td>
<td>0.796</td>
<td>0.720-0.869</td>
<td>37%</td>
</tr>
<tr>
<td>Late PreE</td>
<td>0.796</td>
<td>0.761-0.830</td>
<td>28.9%</td>
</tr>
<tr>
<td>Gest. HTN</td>
<td>0.721</td>
<td>0.677-0.765</td>
<td>26.7%</td>
</tr>
</tbody>
</table>

Maternal Risk Factors for PE

**RISK FACTOR**

- Age > 40
- Nulliparity
- Prior PE
- Family History
- Multiple gestations
- Preexisting IDDM
- Preexisting Hypertension
- Kidney Disease
- Autoimmune Disease
- Antiphospholipid Syndrome
- Obesity (BMI > 26.1)
- Black Race

**RELATIVE RISK (95% CI)**

- Age > 40: 1.68 (1.23-2.29) P0
- Nulliparity: 2.91 (1.28-6.61)
- Prior PE: 7.19 (5.85-8.83)
- Family History: 2.90 (1.70-4.93)
- Multiple gestations: 2.93 (2.04-4.21)
- Preexisting IDDM: 3.56 (2.54-4.99)
- Preexisting Hypertension: 5.2 (1.5-17.2) DBP>110 mmHg (3.2-7.8) DBP>100 mmHg
- Kidney Disease: 5.3%
- Autoimmune Disease: 6.9 (1.1-42.3)
- Antiphospholipid Syndrome: 9.72 (4.34-21.75)
- Obesity (BMI > 26.1): 2.47 (1.66-3.67)
- Black Race: 2.6 (3.2-2.92) Odds Ratio

*Multivariate screening for PE w/MRF
*Time of Delivery for PE treated as a continuous rather than a categorical variable
*Called a competing risk model

Ref: Poon & Nicolaides, Prenatal Diagnosis 2015
System Specific Maternal Risk Profiling

- The Metabolic Risk Profile
- The Cardiovascular Risk Profile
- The Thrombotic Risk Profile
- Placental Risk
- Personal Risk

Applied to high risk patients identified by multimarker testing of placental and personal risk assessment.

Booking Mean Arterial Pressure

- MAP = DBP + 1/3 [SBP minus DBP]
- Combine MAP @ 11-14 weeks with Maternal Factors (MF)
- Prospective Study of 5590 Singleton Pregnancies
- MAP + MF → 62.5% of PE cases
- Screening success better with both compared to either modality by itself
- Basis for all subsequently developed screening strategies

Poon et al. Hypertension 2008;51:1027-1033

First Trimester BP PE Risk Screening

Having first trimester JNC7 prehypertension or hypertension was associated with a 2.18 increased risk of developing PE, whereas normotension was associated with a reduction of risk of 56% in women who initiated low dose aspirin by 16 weeks gestation.

University of Maryland (Baschat)

University of Maryland

Prospective 2441 women
MF (nulliparity, prior HTN, Diabetes, Prior PE, MAP) and PAPP-A MOMs

Early-Onset PE prediction = 55% sensitivity for a 10% false positive rate

<table>
<thead>
<tr>
<th>MAP</th>
<th>&lt;70</th>
<th>&gt;70</th>
<th>0 (0.0%)</th>
<th>6 (0.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-80</td>
<td>2 (0.2%)</td>
<td>50 (4.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-90</td>
<td>12 (1.2%)</td>
<td>85 (8.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Uterine Artery Doppler at 11-13 weeks

Hypertensive disorders in pregnancy: screening by uterine artery Doppler at 11–13 weeks

L. C. Y. POON, I. STABOULIDOU, N. MAIZ, W. PLASENCIA and K. H. NICOLAIIDES
Harri Berghois Research Centre for Fetal Medicine, King’s College Hospital, London, UK

• PROSPECTIVE SCREENING study of
  – Early Pre-eclampsia < 34 weeks (n=37)
  – Late Pre-eclampsia > 34 weeks (n=128)
  – Gestational Hypertension (n=140)
  – Controls (n=8061)
• MULTIVARIATE REGRESSION and ROC
• PREDICTION USING 11-13 6/7 week:
  – Maternal Factors (MF)
  – MF + UAD-PI
First Trimester UAD Plus Maternal Factors

<table>
<thead>
<tr>
<th>Location</th>
<th>Early pre-eclampsia</th>
<th>Late pre-eclampsia</th>
<th>Gestational hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk factor</td>
<td>0.794 (0.720-0.866)</td>
<td>0.796 (0.761-0.830)</td>
<td>0.728 (0.647-0.796)</td>
</tr>
<tr>
<td>Lowest</td>
<td>0.912 (0.863-0.963)</td>
<td>0.912 (0.777-1.047)</td>
<td>0.729 (0.646-0.771)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.902 (0.814-0.993)</td>
<td>0.813 (0.721-0.914)</td>
<td>0.806 (0.707-0.844)</td>
</tr>
</tbody>
</table>

Meta-analysis of 11 first trimester UAD studies/43,122 patients
Prediction of PE = 26% sensitivity, 91% specificity
Overall value of first trimester UAD analysis to predict PE is poor


What is a Biomarker?

A characteristic that is objectively measured and evaluated as an indicator of:
1.) normal biologic processes
2.) pathogenic processes
3.) or pharmacological responses to a therapeutic intervention

Types of Biomarkers

<table>
<thead>
<tr>
<th>Biomarker Type</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antecedent</td>
<td>Identify risk of disease</td>
</tr>
<tr>
<td>Screening</td>
<td>Identify subclinical disease</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>Identifying overt disease</td>
</tr>
<tr>
<td>Staging</td>
<td>Categorizing disease severity</td>
</tr>
<tr>
<td>Prognostic</td>
<td>Predicting recurrence, response to therapy, and monitoring therapy efficacy</td>
</tr>
</tbody>
</table>
What Makes A Good Biomarker?

1) Present in peripheral body tissue and/or fluid (blood, urine, saliva, breath, CSF)
2) Easy to detect/quantify by assay that is affordable and robust
3) Associated with possible damage to particular tissue or disease

Nature Biotechnology 28, 431 (2010)

Uterine Artery Doppler+MF+Biochemical Markers for First Trimester PE Prediction

Poon et al Ultrasound Obstet Gynecol 2010

Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks

L. C. Y. Poon, R. Akolekar, R. Lachmann, J. Beta and K. H. Nicolaides
Karin Bledht Research Centre for Fetal Medicine, King’s College Hospital, London, UK

First Trimester PE Screening: Next Steps

• CASE CONTROL study of
  – Early Preeclampsia < 34 weeks (n=26)
  – Late Preeclampsia > 34 weeks (n=90)
  – Gestational Hypertension (n=85)
  – Controls (n=201)
• MULTIVARIATE REGRESSION & ROC
• PREDICTION USING 11-13 6/7 week INFORMATION:
  – Maternal Factors (MF)
  – MF + Biomarkers (PAPP-A, PI GF, Inhibin-A, Activin-A, TNF-R1, MMP-9, Pentraxin-3, P-Selectin)
  – MF + UAD + MAP
  – MF + UAD + MAP + Biomarkers

Poon et al Ultrasound Obstet Gynecol 2010
First Trimester Multiple Factor Prediction of PE (Multiparametric Testing)

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Early pre-eclampsia</th>
<th>Late pre-eclampsia</th>
<th>Gestational hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum factors</td>
<td>0.71 (0.63–0.77)</td>
<td>0.73 (0.67–0.79)</td>
<td>0.81 (0.70–0.85)</td>
</tr>
<tr>
<td>Serum factors +</td>
<td>0.98 (0.86–1.00)</td>
<td>0.87 (0.70–0.92)</td>
<td>0.75 (0.59–0.80)</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>0.93 (0.82–0.99)</td>
<td>0.85 (0.70–0.97)</td>
<td>0.79 (0.69–0.87)</td>
</tr>
<tr>
<td>Urine Lp, MAP</td>
<td>0.92 (0.82–0.95)</td>
<td>0.86 (0.71–0.93)</td>
<td>0.82 (0.71–0.91)</td>
</tr>
<tr>
<td>Urine Lp, MAP, biomarkers</td>
<td>0.92 (0.82–0.95)</td>
<td>0.86 (0.71–0.93)</td>
<td>0.82 (0.71–0.91)</td>
</tr>
</tbody>
</table>

Estimated detection rates of PE requiring delivery before 34 weeks using MF+biomarkers+UAC+MAP is 96% at false positive rate of 10%.

Angiogenic Markers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive prediction value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIGF</td>
<td>97</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>angiopoietin</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>endostatin</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>VEGF</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>sEng</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
</tbody>
</table>

Biomarkers Summary 2014

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive prediction value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIGF</td>
<td>97</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>angiopoietin</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>endostatin</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>VEGF</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>sEng</td>
<td>96</td>
<td>91</td>
<td>99</td>
</tr>
</tbody>
</table>
Sequential Multiparametric First & Second Trimester PE Screening

- Measure changes in PI GF, sEng & sFlt-1 between 6-15 weeks and 20-25 weeks
- Sensitivity of 100% and specificity of 98% to detect early-onset PE
- Limited clinical utility due to receipt of results late in pregnancy


Other 1st Trimester Biomarkers of PE

- Plasma Endothelin-1
- Free beta-subunit HCG
- IL-1 Beta
- Hydroxy 17 Beta Dehydrogenase
- ADAM12 (A Disintegrin And Metalloproteinase 12
- High sensitivity C-Reactive Protein
- Tumor Necrosis Factor-α
- Interferon-γ
- β-endorphin
- Copeptin
- Podocytes

Maternal plasma [Copeptin] is elevated throughout pregnancy in women who develop preeclampsia.

Control
Preeclampsia

3rd Trimester data similar to Zulfikeroglu et al 2011

Santillan MK, et al Hypertension 2014
Maternal plasma [Copeptin] is predictive of the development of preeclampsia


**Summary**

- Even after controlling important clinical covariates, maternal plasma [Copeptin] is predictive of the development of preeclampsia as early as the 1st trimester (i.e., 6-8 weeks into pregnancy).

- We hypothesize early pregnancy elevations in vasopressin secretion play an initiating role for vasopressin in the development of preeclampsia.

---

Santillan COPEPTIN Human

- Maternal Serum Glycosylated Fibronectin levels in the first trimester are significantly higher in women with PE.
- Remained higher throughout pregnancy.
- Case control study.
- Robust biomarker for monitoring PE.
- No prospective trials/screening/prediction.

---

Receiver operating characteristic curves showing third-trimester PE classification performance of biomarkers within all cohorts
Performance Requirements
PE Prediction/Low Prevalence

- A test to efficiently predict the onset of PE should have:
  - A high positive likelihood ratio (LR+ > 10)
  - A low negative likelihood ratio (LR- < 0.1)

No single combination of factors/markers has reached such a performance level AND been shown prospectively to make a difference in outcome AND with a positive cost/benefit ratio.

COMMITTEE OPINION
Number 538 • September 2015

Committee on Obstetrics Practice
The document has been revised by the Committee on Obstetric Practice. The document reflects current knowledge and scientific evidence. It does not represent the views of the American College of Obstetricians and Gynecologists.

First-Trimester Risk Assessment for Early-Onset Preeclampsia

**ABSTRACT:** Hypertensive disorders with adverse sequelae including preterm birth, maternal morbidity and mortality, and long-term risk of maternal cardiovascular disease constitute 5-10% of pregnancies. Early identification of pregnant women at risk of developing antenatal preeclampsia would theoretically allow referral for more intensive surveillance or application of preventive therapies to reduce the risk of severe disease. In practice, however, the incremental or cost-benefit would be limited by the low positive predictive value for early-onset preeclampsia reported in the literature. In light of the modest predictive value of first-trimester preeclampsia risk assessment and the lack of data demonstrating improved clinical outcomes, commercial tests are being marketed for the prediction of preeclampsia in the first trimester. Given a robust medical history to evaluate for risk factors in pregnancy, the best and only recommended screening approach for preeclampsia is the method of screening for preeclampsia until studies show that aspirin or other interventions reduce the incidence of preeclampsia for women at high risk based on first-trimester predictors need.

**Box 1. Clinical Risk Factors for Preeclampsia**

- Primiparity
- Previous preeclamptic pregnancy
- Chronic hypertension, chronic renal disease, or both
- History of thrombophilia
- Multifetal pregnancy
- In vitro fertilization
- Family history of preeclampsia
- Type I diabetes mellitus or type II diabetes mellitus
- Obesity
- Systemic lupus erythematosus
- Advanced maternal age (older than 40 years)

SYSTEMS BIOLOGY APPROACH

• Integration of automated platform technologies that can process multivariate and multiplex data
• High dimensional biology = "omics" to obtain a holistic evaluation of the molecules constituting an organ/organ system
• Old and new "omics":
  – genomics (study genes)
  – messenger RNA (transcriptomics)
  – proteins (proteomics)
  – Metabolites (metabolomics)
  – Methylation profiling (epigenetics)
  – Nanovesicles
  – lipidomics


L Bond et al (Metabolomic Diagnostics/Ireland): Preeclampsia Risk Stratification Early in Pregnancy: Levering a Promising Metabolomics Discover in a LC-MS based Clinical Assay

• ISSHP Poster 2015
• Simple metabolite (40) extraction and a targeted LC-QqQ-MS (quadruple mass spectrophotometers/10 minutes) approach using stable isotope labelled metabolites for relative quantification has been developed
• Public-private biobanking efforts
• Being tested now in clinically relevant patient groups

For PE risk prediction...
* Data for prepregnancy screening are limited
* Predictive performance of first trimester prediction models utilizing risk factors and clinical data are insufficient to recommend routine screening of a healthy nulliparous population (future work incorporating biomarkers into these models is warranted)
* Multiple trimester testing of biomarkers + clinical parameters?
* Issues with cost, patient acceptibility, etc
* Single biomarker testing unlikely to be useful—multiple markers
First trimester prediction algorithms for PE share a high negative predictive value if applied to an external population (high specificity)....

These algorithms underperform in their ability to correctly identify women who develop PE (low sensitivity)....

**AT THIS TIME**

- Risk Assess the Mother for PE
- Baseline/First Trimester Mean Arterial Pressure (MAP) \( \geq 90 \) mmHg
  
  MAP = DBP plus 1/3 of the pulse pressure (SBP-DBP=PP)

  Example: BP of 130/85 \( \Rightarrow \) MAP is 85 plus 1/3 of 130-85 or 15 \( \Rightarrow \) MAP = 100

**First Trimester Screening for Early Onset Preeclampsia**

“The Predicament of the Prediction and Prognostication of Preeclampsia”

James N Martin Jr